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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/009,950	12/14/2001	Akira Nakamura	31671-176197	7278

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EXAMINER

BERTOGLIO, VALARIE E

ART UNIT

PAPER NUMBER

1632

DATE MAILED: 10/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/009,950	NAKAMURA ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
  - If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
  - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
  - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 18 August 2004.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1 and 3 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1 and 3 is/are rejected.
- 7) ☒ Claim(s) 3 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 14 December 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                                   | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)               | Paper No(s)/Mail Date. _____  |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>08/18/2004</u> .  | 6) <input type="checkbox"/> Other: _____                                    |

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### **DETAILED ACTION**

Applicant's amendment filed 08/18/2004 has been received. Claims 1 and 3 have been amended. Claims 2 and 4-11 have been cancelled. Claims 1 and 3 are pending and under consideration in the instant office action.

#### ***Claim Objections***

Claim 3 is objected to because of the following informalities: Claim 3 appears to have a typographical error in line 13. It reads "FcRIIB" rather than "FcγRIIB".

Appropriate correction is required.

#### ***Claim Rejections - 35 USC § 112-1<sup>st</sup> paragraph***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

In light of Applicant's amendments to the claims limiting the claimed animal model to a non-chimeric homozygous mouse exhibiting a specific and useful phenotype, the enable rejection set forth on pages 2-8 of the previous office action is withdrawn.

However, a new grounds of rejection based on the amendments appears below.

Claims 1 and 3 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse whose genome comprises a homozygous disruption of the exons encoding S<sub>2</sub> and EC<sub>1</sub> of the FcγRIIB gene wherein immunization of said transgenic mouse with type IV collagen results in a mouse model of Goodpastures syndrome exhibiting diffuse alveolar hemorrhage, glomerulonephritis and the appearance of antikidney glomerular basement membrane antibody and for a method of using the claimed mouse to screen for potential remedies wherein a treated mouse

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model is compared to an untreated mouse model, does not reasonably provide enablement for and destruction or deficiency of the FcγRIIB gene or for mice exhibiting only a subset of the claimed phenotypes or for methods of screening by comparing a treated model mouse or a treated wild-type mouse. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 1 is directed to a mouse model of Goodpastures syndrome wherein the genome of the mouse comprises a disruption of the FcγRIIB gene and is immunized with type IV collagen resulting in a phenotype of diffuse alveolar hemorrhage, glomerulonephritis or the appearance of antikidney glomerular basement membrane antibody. Claim 3 encompasses a method of using the claimed mouse for screening for remedies for symptoms of Goodpastures syndrome that are exhibited by the mouse. The claim requires comparing the treated mouse model of Goodpastures syndrome to a treated wild-type mouse.

The breadth of the claims is such that they encompass genetic mutation of the FcγRIIB gene by any type of destruction, deficiency or substitution. However, the specification and the art of record teach only substitution of the exons S<sub>2</sub> and EC<sub>1</sub> with a neo gene cassette (see specification page 9, paragraph 3; Takai, 1996, Nature, Vol. 379, page 347, Figure 1a, IDS). The specification does not teach any other sort of genetic disruption involving the FcγRIIB gene. Other gene disruptions, including substitution of other domains or exons will not necessarily cause the same change in activity of the FcγRIIB gene product as the disruption taught by the specification. It cannot be predicted what activity level and what phenotype a resulting mouse would have with any other

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gene disruption. Therefore, it would require undue experimentation for the skilled artisan to make the claimed mouse having any type of destruction, deficiency or substitution other than substitution of the exons S<sub>2</sub> and EC<sub>1</sub> with a neo gene cassette as taught by the instant specification.

The claims also contain Markush language. Therefore the breath of the claims encompasses mice exhibiting any subset of the phenotypes including diffuse alveolar hemorrhage, glomerulonephritis and the appearance of antikidney glomerular basement membrane antibody. The specification teaches that the claimed mice exhibited each of these phenotypes and does not teach that they exhibit only one or two of the phenotypes. As set forth on page 5 of the previous office action, the phenotype of transgenic knockout mice unpredictable and it cannot be determined based on the teaching in the instant specification and the art of record, how to make the claimed mouse exhibiting only a subset of the claimed phenotypes.

Claim 3 is not enabled because it compares the model mouse treated with a potential remedy to a wild-type mouse treated with the same compound. The specification does not teach what results would indicate an effective remedy using these method steps. The specification does not teach what to compare. The skilled artisan would know how to carry out the claimed method wherein the effect of the potential remedy on the claimed phenotypes is compared to a model mouse that is not treated with the potential remedy. It would require undue experimentation to determine how to screen for remedies for Goodpastures syndrome by comparing the claimed model mouse to a wild-type mouse, wherein both mice are treated with a potential remedy.

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Therefore, based on the breadth of the claims, the unpredictability of phenotype in knockout mice and the lack of guidance in the specification with respect to the combination of phenotypes and types of gene disruption encompassed by the claims, it would require undue experimentation to determine how to make the claimed animal with a reasonable expectation of success.

***Claim Rejections - 35 USC § 112-2<sup>nd</sup> paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claim 3 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained.

Claim 3 is incomplete as written. The preamble is directed to a method for screening for a remedy for Goodpastures syndrome. However, the claim is incomplete because the method steps fail to relate back to the preamble in a positive process. Applicant did not amend the claim with respect to this rejection. The final step of the claim is not complete because it does not set forth how the comparative evaluation will indicate a remedy.

Claim 3 is also unclear because it refers to diffuse alveolar hemorrhage and presence of antikidney glomerular basement membrane antibody as disease. These are not diseases but are symptoms.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

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(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Takai (1996, Nature, Vol. 379, pages 346-348; IDS) in view of Abbate, (1998, Kidney International, Vol. 54, pages 1550-1561; IDS) or Kalluri (1994, PNAS, Vol. 91, pages 6201-6205;IDS).

Claim 1 is drawn to a mouse model of Goodpastures syndrome wherein the genome of the mouse comprises a homozygous disruption of the Fc $\gamma$ RII gene and upon immunization with type IV collagen the mouse exhibits diffuse alveolar hemorrhage, glomerulonephritis or the appearance of antikidney glomerular basement membrane antibody.

Takai taught knocking out the Fc $\gamma$ RII gene in mice results in increased humoral and anaphylactic responses in the mice in response to antigens including sheep red blood cell, trinitrophenol keyhole limpet haemocyanin and trinitrophenol lipopolysachharide or TNP-Ficoll. Takai taught that the Fc $\gamma$ RII gene encodes a low-affinity immunoglobulin-G receptor that acts as a general negative regulator of immune-complex triggered immune system activation. Loss of this negative-regulator increased humoral and anaphylactic responses in the mice because the mice lack an ability for regulation of antibody level in response to antigenic stimulation (page 347, col. 1, last paragraph). Takai did not teach immunizing Fc $\gamma$ RII-deficient mice with type IV collagen.

However, Abbate taught immunizing wild-type rats with  $\alpha$ 3 type IV collagen causing experimental Goodpastures syndrome characterized by pulmonary hemorrhage

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involving alveolar capillaries, crescentic glomerulonephritis, deposits of IgG along glomerular basement membranes (for example, see page 1560, col. 1, last para.). Similarly, Kalluri taught immunizing rabbits with the NC1 subdomain of  $\alpha 3$  type IV collagen causing formation of autoantibodies that lead to a mimicking of human Goodpastures syndrome (page 6201, col. 1). Both Abbate and Kalluri taught that Goodpastures Syndrome is an autoimmune disease characterized by pulmonary hemorrhage and glomerulonephritis and anti-glomerular basement membrane auto-antibodies.

It would have been obvious to one of skill in the art at the time the application was filed to immunize the Fc $\gamma$ RII knockout mice taught by Takai with type IV collagen antigen as taught by Abbate and Kalluri. One of skill in the art would have been motivated to combine the teachings of Takai, Abbate, and Kalluri because it was known that type IV collagen is an antigen known to cause the auto-immune reactivity responsible for Goodpastures syndrome and that the Fc $\gamma$ RII knockout mice lack a negative regulatory response to various antigens that may contribute to the development of autoimmunity. This the combination of the Fc $\gamma$ RII knockout mouse with the immunization with type IV collagen allows for mouse model of Goodpastures syndrome known to have greater autoimmune-reactivity, a characteristic of human Goodpastures syndrome.

Thus, the claimed invention is clearly *prima facie* obvious in the absence of evidence to the contrary.

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***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Valarie Bertoglio  
Examiner  
Art Unit 1632

*Joe Waitland*  
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